REMARKS

Currently Claims 1-28 are pending and stand rejected under the Office Action mailed June 1, 2006. Applicants have amended independent Claims 1 and 28 above, canceled Claim 17 for consistency with the Amendment to Claim 1, and added new Claims 55 and 56 to more fully claim what Applicants perceive to be the scope of the present invention. In view of the above amendment and the following remarks, reconsideration is respectfully requested.

Elected Claims

Applicants acknowledge that Claims 4-5, 9, 17-18, 20, 22, 24-25 and 27 are withdrawn as being directed to a non-elected species, but depend from a generic claim. Applicants note that dependent Claim 8 should also be withdrawn as directed to a non-elected species, and likewise depends from a generic claim.

Specification

The undersigned attorney has reviewed the instant specification and confirms that all references that are expressly incorporated by reference therein were published US Patents or published International Patent Applications at the time of filing of the instant application.

Information Disclosure Statement

Applicants noted that a number of previously submitted references mailed with prior information disclosure statements were evidently not received by the Examiner. Applicants have resubmitted copies of these references, together with additional art in keeping with Applicants' continuing duty of disclosure.

New Claims

Applicants note that new Claim 55 is identical to Claim 1, except that it does not call for continuous irrigation, and is directed specifically to intraocular procedures and the irrigation of intraocular tissues. Claim 56 is identical to Claim 1, except that it is directed specifically to

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intraocular procedures and the irrigation of intraocular tissues and does not specifically require an IOP reducing agent or a mydriatic agent.

Rejection under 35 USC § 102 Based on Cagle et al.

Claims 1-3 and 12-15 were rejected under 35 USC § 102(b) based on WO 95/16435 to Cagle et al. Applicants respectfully traverse the rejection. Cagle discloses irrigation solutions including nonsteroidal anti-inflammatory drugs (NSAIDs), such as cyclooxygenase and lipoxygenase antagonists. (Cagle, page 7, lines 27-28). Although it is stated that the solutions may perform multiple functions including modulating intraocular pressure or preventing surgically induced miosis, the objective of the solutions is to prevent or treat ophthalmic inflammation associated with surgery. (Cagle, page 6, line 28 – page 7 line 15). The only pharmacologic agents disclosed for inclusion in the solution are NSAIDs (page 7, line 27 – page 8, line 30). Cagle does disclose the inclusion of a free radical scavenger, such as glutathione, electrolytes, an energy source such as dextrose, bicarbonate and buffers. These additional ingredients are part of the irrigation solution carrier commonly sold as BSS Plus® (Cagle, page 9), and are not typically considered medications or active pharmaceutical ingredients. There are no disclosed mydriatic agents or agents for decreasing intraocular pressure. In summary, Cagle discloses NSAID solutions in an otherwise non-medicated BSS Plus® carrier.

In contrast, Claim 1 of the present invention is directed to a method of perioperatively delivering a solution including at least first and second therapeutic agents, selected from anti-inflammatory agents, analgesic agents, mydriatic agents or IOP reducing agents, with the second agent providing at least one of these therapeutic functions different that the function(s) provided by the first agent. As amended above, Claim 1 also recites that one of the agents in the solution must be a mydriatic agent or an IOP reducing agent. Cagle does not disclose the use of any

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pharmacologic agents other than anti-inflammatory agents, and specifically does not disclose the use of a mydriatic agent or an IOP reducing agent.

Applicants also disagree with the Examiner's interpretation of "irrigate" as necessarily meaning "continuously irrigate." Applicants submit with the accompanying information disclosure statement an excerpt from *Taber's Cyclopedic Medical Dictionary*, 19th Edition (2001), which provides the following definitions:

irrigate: "To wash out with a fluid"

irrigation: "The cleansing of a canal by flushing with water or other fluids; the washing of a wound..."

bladder i.: "Washing out of the bladder to treat inflammation or infection or to maintain patentcy of a urinary catheter..."

continuous bladder i.: "A constant flow of normal saline or another bladder irrigant through a three-way urinary catheter to keep the catheter patent..."

As evidenced by *Taber's*, the term "irrigation" does not necessarily imply "continuous irrigation"; rather, "continuous" is conventionally used by those of skill in the medical field as an adverb to modify "irrigation". Thus Applicants submit that Cagle does not disclose "continuous" irrigation. Applicants also note that, with respect to the instant invention of Claim 1, the term "continuous" is intended to be construed as expressly defined on page 6, lines 25-32 of the instant specification. As so construed, Cagle does not disclose continuous irrigation.

In summary, Cagle is very distinct from the method of Claim 1, disclosing NSAID solutions rather than methods of using solutions including multiple therapeutic agents, with at least one of the agents being an IOP reducing agent or a mydriatic agent, and also failing to disclose continuous irrigation.

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Rejection under 35 USC § 102 Based on Gan

Claims 1, 6 and 8 also stand rejected under 35 USC § 102(b) based on US 5,523,316 to Gan et al. Applicants respectfully traverse this rejection. Gan discloses irrigation solutions including one or more drugs for controlling intraocular pressure in a BSS Plus® carrier solution. However, Gan does not teach combining the IOP reducing agent(s) with another agent that is an anti-inflammatory, analgesic or mydriatic agent, as claimed. Referring again to *Taber's*, disclosure of irrigation by Gan does not imply continuous irrigation. For these reasons, the rejection based on Gan should be withdrawn.

Gan and Cagle are both examples of disclosures that fall short of the present invention. Cagle teaches solutions for controlling inflammation. Gan teaches solutions for controlling IOP. Neither teaches solutions of multiple agents selected to control multiple physiologic functions associated with ophthalmologic surgery.

Rejection under 35 USC § 103 Based on Thomas

Claims 1-3, 6-8, 10-16, 19, 23, 26 and 28 stand rejected under 35 USC § 103(a) based on US Patent 5,811,446 to Thomas. The Examiner characterizes Thomas as disclosing ophthalmic histidine solutions but as not disclosing continuous irrigation or an exemplary method utilizing a composition comprising an NSAID or a steroid, timolol, and phenylephrine. The Examiner concludes that it would be obvious to modify Thomas to overcome these shortcomings. Applicants respectfully traverse the rejection.

As acknowledged by the Examiner, Thomas fails to disclose continuous irrigation during an ophthalmologic procedure, which is a limitation of present Claims 1 and 56. Moreover, Thomas actually teaches away from continuous irrigation. Thomas discloses that "The ophthalmic histidine solutions of the present invention are administered topically by applying them to the cul-de-sac of the eye from a dropper controlled bottle or dispenser. A typical dose

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regimen for an adult human may range from about 2 to about 8 drops per day (about 0.1 mg to about 10.0 mg of histidine). Dosages for adult humans may, however, be as high as about 100 mg histidine per day, in which case the drops are administered by "bunching", e.g., 5 doses administered over a 5 minute period, repeated 4 times daily." (Column 9, lines 50-68). Thomas also briefly discloses a topical artificial tear formulation, ophthalmic ointments, sustained release ocular inserts, intraocular injection, intravenous administration and oral administration. (Column 9, line 59-Column 11, line 14).

Thomas teaches that solutions are administered drop wise to the eye, rather than by continuous irrigation. Continuous irrigation with the disclosed compositions would also greatly exceed the disclosed dosage of histidine. Thomas thus teaches away from continuous irrigation as claimed in independent Claims 1 and 56. Ocular solutions that are administered drop wise conventionally include a preservative, due to the possibility of contamination or decomposition associated with multiple applications from a dispenser, and replacement of solution within the container with air, over time. Presumably for this reason, Thomas discloses that preservatives may be included in the histidine compositions (Column 9, lines 23-38). However, the use of preservatives in solutions applied to the eye during surgical procedures can be problematic due to toxicity concerns. This is particularly the case for intraocular surgery, in which preservatives have been associated with corneal toxicity. See, e.g., Eleftheriadis, H. et al., *Corneal Toxicity Secondary to Inadvertent Use of Benzalkonium Chloride Preserved Viscoelastic Material in Cataract Surgery*, British Journal of Ophthalmology 86:299-305 (2002), included with the information disclosure statement provided herewith. The topical solution disclosed by Thomas would be inappropriate for use in the intraocular procedures of independent Claims 55 and 56.

Independent Claim 28 calls for a method of perioperatively inhibiting inflammation, inhibiting pain, effecting mydriasis and/or decreasing IOP by delivering first and second agents

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selected to perform different physiologic functions as previously described, wherein each agent is included at a concentration of no more than 100,000 nanomolar. This is a very dilute solution, as is appropriate for perioperative irrigation. In contrast, Thomas discloses histidine solutions including 0.01 to about 30% be weight histidine (Column 8, lines 47-48) and other agents that may be optionally included at 0.3-20% by weight (Column 7, lines 1-11). A 0.01% to 30% by weight histidine solution is equivalent to a 640,000 to 1,920,000,000 nanomolar histidine solution, well in excess of that claimed. Such high concentrations are suitable for topical drop wise application, but would be inappropriately high for perioperative irrigation.

In sum, Thomas teaches topical ophthalmologic solutions administered drop wise to the eye. It would not be appropriate to modify Thomas to use these solutions for continuous irrigation, for intraocular irrigation, or to provide dilute solutions of less than 100,000 nanomolar. The high concentrations and preservatives of the Thomas solutions would make them inoperative for such usages.

Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 1-28 are rejected for nonstatutory obviousness-type double patenting based on various claims of: US Patents 6,056,715, 5,820,583 and 6,210,394, all in view of Thomas; US Patents 6,261,279, 6,413,961 and 6,420,432; and US Patent 6,254,585. Each of these noted US Patents (excluding Thomas) was issued to inventors Demopulos et al. and assigned to the assignee of the current application. The Demopulos patents each claim perioperative methods for inhibiting pain and/or inflammation during surgical procedures, or solutions for inhibiting pain and/or inflammation, using one or a plurality of anti-inflammatory/anti-pain agents. The particular agents claimed vary for each of these patents. However, in all cases the agents claimed are anti-inflammatory and/or anti-pain agents. In no cases are mydriatic agents or agents for reducing intraocular pressure claimed in the noted Demopulos patents. Applicants

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have amended Claims 1 and 28 to reflect this distinction, which is also reflected in new Claim 55.

Further, the methods of the presently pending claims would not be obvious over the claims of the Demopulos patents, which are directed solely to pain and inflammation and not to reducing IOP and or promoting mydriasis as required by Claims 1, 28 and 55 and permitted by Claim 56. Consideration of Thomas does not change this outcome, as Thomas is directed to concentrated ocular solutions applied drop wise to the eye. As such, applicants submit that the obviousness-type double-patenting rejections should be withdrawn.

Closure

Reconsideration and allowance of all pending claims, inclusive of Claims 1-16, 18-28, 55 and 56 is respectfully requested. Should the Examiner have any questions or wish to discuss any matter, he is invited to telephone the undersigned attorney.

Respectfully Submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

12-01-06
Date

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